REMARKS

In view of the following remarks, the Examiner is requested to allow claims 1, 3-5, 8, 10-28, 30-33, and 45, the only claims under examination in this application.

Claims 1 and 45 have been amended to recite that the specific association enhancer is a cationic detergent and to recite the total ionic salt concentration as less than 50 mM. Support for these amendments can be found in original Claim 2 and in the specification, particularly at page 25, lines 15-19. Claim 2 has been canceled. Claims 3 and 5 have been amended to depend upon Claim 1 by virtue of the cancellation of Claim 2.

No new matter has been added.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 10-14, 25, 26, 28, 30, and 45 were rejected under 35 U.S.C. § 102(b) as allegedly being clearly anticipated by Kim *et al. Antisense Res Dev* **1995**, *5*:49-57. This rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The present claims recite a hybridization reaction performed in the presence of a cationic detergent. Kim *et al.* does not disclose the presence of a cationic detergent in a hybridization reaction, and the Examiner has not rejected over Kim *et al.* the claims that recite cationic detergents. Accordingly, because Kim *et al.* does not identically disclose each and every element of Applicants' claims, there is no anticipation. Withdrawal of this rejection is respectfully requested.

Claims 1-5, 10-14, 25, 26, 28, 30, and 45 were rejected under 35 U.S.C. § 102(e) as allegedly being clearly anticipated by Kolesar *et al.* (U.S. Patent No. 6,013,442). This rejection is respectfully traversed.

The Examiner has directed attention to Example 1 of Kolesar *et al.* for an alleged teaching of the stabilization of RNA-DNA duplexes in a hybridization reaction by the inclusion of CTAB in the nucleic acid molecular hybridization reaction. Example 1 of Kolesar *et al.* discloses hybridization wherein the buffer contains 50 mM NaCl. Therefore, the total ionic salt concentration is at least 50 mM. In

contradistinction, the present claims recite a total ionic salt concentration of less than 50 mM. Accordingly, because Kolesar *et al.* does not identically disclose each and every element of Applicants' claims, there is no anticipation. Withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 2-5, 8, 15-24, 27, and 31-33 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kim *et al.*, *supra*, in view of Cronin *et al.* (U.S. Patent No. 6,027,880). This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed method. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (MPEP § 2143). The teaching or suggestion to arrive at the claimed method and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (MPEP § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

The Examiner asserted that Cronin *et al.* teaches the hybridization of multiple nucleic acids on arrays to detect single nucleotide differences, and he directed attention to columns 38-42. However, the cited sections of Cronin *et al.* do not detect single nucleotide differences in RNA-DNA duplexes nor does Cronin *et al.* disclose the use of CTAB as a specific association enhancer.

Furthermore, Applicants have found that CTAB accelerated the formation of DNA:DNA duplexes of a pair of 20 nucleotide DNA oligis more than 300-fold, but had no observable effect on discrimination between completely matched DNA:DNA duplexes and DNA:DNA duplexes with a single nucleotide mismatch at any position along the oligo (See Example 1, Table 1). In contrast, using the same complementary pair of oligos under standard, non-accelerated conditions, but with RNA and DNA, improved the selectivity of formation of matched RNA:DNA duplexes over RNA:DNA duplexes with a single nucleotide mismatch (See Example 1, Table 1).

Unexpectedly, Applicants have found that addition of CTAB for acceleration of RNA:DNA duplex formation further increased discrimination against single nucleotide mismatched duplexes at all positions, as compared to standard non-accelerated conditions (See Example 1, Table 1). Using a second, enzymatic assay for duplex detection showed that, in the presence of CTAB, the association of

DNA and RNA molecule had up to a 50-fold enhancement of specificity (See Example 2, Table 2). The effect of CTAB in enhancing specificity of association is independent of the DNA or RNA molecule, and is affected only by the length of the region of complementarity. The effect of CTAB is also independent of the of the nucleotide composition of the DNA and RNA molecules.

In addition, CTAB is known to reduce "background signal" in hybridizations. See, for example, U.S. Patent No. 6,040,138 (US'138) at Column 22, lines 17-24, a copy of which is provided for the Examiner's convenience. The US'138 indicates at Column 7 that the "terms 'background' or 'background signal intensity' refer to hybridization signals resulting from non-specific binding, or other interactions, between the labeled target nucleic acids and components of the oligonucleotide array (e.g., the oligonucleotide probes, control probes, the array substrate, etc.)." Specifically, the US'138 patent states at Column 27, lines 25-31:

> It was discovered that the excess RNA in the sample frequently bound up the high density array probes and/or targets and apparently prevented the probes from specifically binding with their intended target. This problem was obviated by hybridizing at temperatures over 30°C and/or adding CTAB (cetyltrimethylammonium bromide) a detergent.

Thus, there was an understanding at the time of the present invention that CTAB was useful to prevent non-specific binding of the RNA to the array. Absent a disclosure of the use of CTAB as a specific association enhancer in Cronin *et al.*, one would presume that CTAB is being used in the hybridization procedure of Cronin *et al.* for its known use to reduce background signal.

Therefore, for at least the reason that the combination of the cited documents does not teach suggest all the elements of Applicants' claims, and further because of Applicants' unexpected results, there is no *prima facie* obviousness. Withdrawal of this rejection is respectfully requested.

Claims 8, 15-24, 27, and 31-33 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kolesar *et al.*, *supra*, in view of Cronin *et al.*, *supra*. This rejection is respectfully traversed.

The rejected claims depend directly or indirectly upon Claim 1, which now recites a total ionic salt concentration of less than 50 mM. As noted above with respect to the rejection under 35 U.S.C.

§ 102(e) over Kolesar *et al.*, Kolesar *et al.* does not disclose a total ionic salt concentration of less than 50 mM. Because Cronin *et al.* was cited by the Examiner for allegedly teaching the hybridization of multiple nucleic acids on arrays to detect single nucleotide differences, Cronin *et al.* does not remedy this deficiency of Kolesar *et al.*

Therefore, for at least the reason that the combination of the cited documents does not teach suggest all the elements of Applicants' claims, there is no *prima facie* obviousness. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-202.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 14/06/06

By: _____
Richard A. Schwartz
Registration No. 48,105

Enclosure: Courtesy copy of U.S. Patent No. 6,040,138

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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